



# Treatment of Metastatic Non-Small Cell Lung Cancer: A Systematic Review of Comparative Effectiveness and Cost-Effectiveness

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## PREFACE

Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of QUERI Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at [nicole.floyd@va.gov](mailto:nicole.floyd@va.gov).

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## EXECUTIVE SUMMARY

### BACKGROUND

Lung cancer is the leading cause of cancer death in both men and women in the United States. Most patients with lung cancer are diagnosed when the cancer is already advanced (stage III or IV), and they are no longer candidates for surgical resection. Small cell lung cancer and non-small cell lung cancer (NSCLC) are treated as different diseases in terms of therapy. In the last few years, several novel agents aimed at specific molecular targets have been developed. This review was requested to evaluate the current evidence on the effectiveness and cost-effectiveness of treatments for advanced NSCLC.

The key questions were:

Key Question #1. For patients with metastatic non-small cell lung cancer (NSCLC) what is the comparative effectiveness of the different recommended (e.g. NCCN guidelines) first line chemotherapy regimens?

Key Question #2. For patients with metastatic NSCLC what is the comparative effectiveness of the different recommended (e.g. NCCN guidelines) second line chemotherapy regimens?

Key Question #3. For patients with metastatic NSCLC what is the benefit of maintenance therapy following first line chemotherapy regimens compared with no maintenance therapy?

Key Question #4. What is the relative cost and cost-effectiveness of the different approaches in Key Questions 1-3?

### METHODS

We employed a two-step search strategy. The first step was to identify recently published systematic reviews; we searched PubMed and Cochrane databases for systematic reviews and cost-effectiveness analyses from 1/1/1966 through 3/16/2012, using standard search terms relating to advanced non-small cell lung cancer and cost-effectiveness analyses. The second step was to identify relevant clinical trials, which we identified by searching Medline (OVID), Embase, and Cochrane Register of Controlled Trials from 1/1/2007 through 5/8/2012, using search terms such as randomized controlled trial, carcinoma, non-small-cell, gemcitabine, etc. We limited both searches to peer-reviewed, English language literature. We also obtained a list of key publications from the technical expert panel. Additionally, systematic reviews identified in the first search were reference mined for relevant trials.

For systematic reviews and cost-effectiveness analyses to be included, they either had to present a systematic review or cost-effectiveness analysis, and had to present data on metastatic NSCLC, either for a range of stages, or more specifically for stage III, IV, or advanced NSCLC. The systematic reviews also had to assess a first line, second line, or maintenance therapy. Exclusion criteria included duplicate publications, not presenting data on NSCLC, presenting data only for stage I or II NSCLC, or not capturing treatments of interest for the systematic reviews. We did not exclude studies based solely on having assessed a drug not in current NCCN guidelines,

as guidelines can change and in part do so in response to systematic reviews of evidence. To be included trials had to address first line, second line, or maintenance therapy for advanced non-small cell lung cancer.

## DATA SYNTHESIS

For Key Question #1 (first-line therapy), we identified an existing systematic review which was both comprehensive and good quality, and used this article as the basis for presenting data pertinent to first-line therapy. This report was divided into sub-questions, into which we sorted the systematic reviews and trials identified by our search strategies. For Key Question #2 (second-line therapy), we created three evidence tables and narratively summarized the findings. The first evidence table presents data for the relevant systematic reviews, the second maps all relevant identified trials to the systematic reviews, and the final evidence table presents more detailed data for trials not included in the existing identified systematic reviews. For Key Question #3 (maintenance therapy), we identified a good quality, comprehensive recent review. Analogous to what was done for first-line therapy, we searched for new relevant trials in addition to the existing review. The first evidence table presents data for the relevant systematic reviews and the second presents data for relevant identified trials not included in the existing systematic reviews. For Key Question #4 (cost-effectiveness analyses), evidence table data are organized by therapy type. After obtaining input from our TEP, we focused on specific cost-effectiveness analyses of greatest interest.

## PEER REVIEW

A draft version of this report was reviewed by four technical experts, as well as clinical leadership. Reviewer comments were addressed and our responses were incorporated in the final report.

## RESULTS

We screened 736 titles for systematic reviews and cost-effectiveness analyses and 820 titles for trials. We screened 88 potential systematic reviews and cost-effectiveness analyses in more detail. From these, we identified 55 articles for inclusion: 24 were relevant to Key Question #1, 6 were relevant to Key Question #2, 3 were relevant to Key Question #3, and 22 were cost-effectiveness analyses relevant to Key Question #4. From the trial citations, 120 were potential includes after the title screen. Of the 60 meeting final inclusion criteria, there were 43 articles relevant to Key Question #1, 14 relevant to Key Question #2, and three relevant to Key Question #3. Peer review identified ten additions, including four trials for Key Question #1, one systematic review and two trials for Key Question #2, and one update on a trial already included for Key Question #3, as well as one new trial.

### Key Question 1. First-line therapy

- **Key Sub-question 1.1.** New trials continue to support the conclusion by the CCO that any differences in survival between platinum-based doublets are modest (GRADE=high).

- **Key Sub-question 1.2.** This result continues to support the conclusions by the CCO that doublet chemotherapy including a platinum agent has a higher survival rate and a higher response rate than a single agent (GRADE=high).
- **Key Sub-question 1.3.** New trials continue to support the conclusion by Goffin and colleagues that any differences in outcomes between platinum-based agents are modest (GRADE=high).
- **Key Sub-question 1.4.** New trials continue to support the conclusion by the CCO that doublet chemotherapy including a platinum agent probably has a slight advantage over nonplatinum doublets (GRADE=moderate).
- **Key Sub-question 1.5.** One new trial does not alter the conclusion by the CCO that cisplatin combinations may have a slight advantage over carboplatin combinations in terms of survival and response rate. However, carboplatin generally has a milder toxicity than cisplatin (GRADE=moderate).
- **Key Sub-question 1.6.** New trials continue to support the review by the CCO that triplet cytotoxic therapy might have some slight advantages in terms of response rate but at an increased risk of toxicity (GRADE=high).
- **Key Sub-question 1.7.** New trials of a number of novel targeted agents have so far failed to find results equivalent to the increases in progression-free survival seen with erlotinib (mostly in patients who have never smoked) and bevacizumab (in an Asian population subgroup analysis) in the CCO review (GRADE=moderate).
- **Key Sub-question 1.7.1** Erlotinib or gefitinib monotherapy is in general superior in terms of beneficial outcomes and adverse events than cytotoxic chemotherapy in patients with EGFR mutations (GRADE=high).
- **Key Sub-question 1.12.** With the exception of studies of gefitinib and erlotinib monotherapy (in patients with EGFR mutations), doublet chemotherapy probably has a slight benefit in terms of survival compared to singlet therapy, but causes more toxicity (GRADE=moderate). Also, there now has been one trial of platinum therapy in the elderly taken to completion that found a near-doubling of the proportion of patients alive at one year in the doublet therapy group compared to monotherapy.

### Summary of Key Question 2: Second-line therapy

The conclusions from the relevant systematic reviews can be summarized as:

- doublet second line cytotoxic therapy might offer slight benefits in progression-free survival and response rate, not overall survival, but at a cost of increased toxicity;
- erlotinib produces modest increases in overall survival; and
- in one phase II study, the addition of bevacizumab to second line treatment resulted in improvements in survival that were not statistically significant.

The summary of these trials not included in existing systematic reviews is:

- Considering data from first line and maintenance therapy studies in addition to second line studies, there are sufficient data to support the conclusion that histology type influences the effectiveness of potential treatments. Pemetrexed is more effective in nonsquamous NSCLC, while docetaxel is more effective in squamous NSCLC (GRADE=moderate).

- Tyrosine kinase inhibitors, when used as second-line therapy in patients unselected for EGFR mutation status, produce overall survival similar to docetaxel (GRADE=strong).
- There is insufficient data to support effectiveness of other drugs, or drugs in combinations, in second-line therapy (GRADE=moderate).
- The above second line studies are typically undertaken after evidence of disease progression, and should be distinguished from maintenance therapy, which is undertaken when a patient has at least stable disease during treatment (typically four cycles).

### Summary of Key Question 3: Maintenance Therapy

- Maintenance therapy improves overall survival (GRADE=high).
- Maintenance therapy with gefitinib significantly prolonged preprogression-free survival compared with placebo in patients from east Asia with advanced NSCLC who achieved disease control after first-line chemotherapy (GRADE=high).
- There is insufficient evidence to reach conclusions regarding whether a continuous or a switch strategy is superior (GRADE=very low). However, two drugs have been approved for switch therapy.
- Differences in survival in placebo-controlled trials of erlotinib or cytotoxic agents are sufficiently small that head-to-head comparisons will be required before strong conclusions can be reached about comparative effectiveness.

### Summary of Key Question 4: Cost-Effectiveness Analyses

There are a large number of published cost-effectiveness analyses, but approximately two-thirds of such studies are supported by the makers of the drugs being assessed. Invariably, studies supported by the makers concluded that their drug was cost-effective. Of the cost-effectiveness analyses not supported by industry, the addition of bevacizumab to first-line therapy was found in one study to be not cost-effective, erlotinib was found in one study to be marginally cost-effective, and the differences between erlotinib and docetaxel maintenance therapy were slight in another study (GRADE=low).

## ABBREVIATIONS TABLE

CI	Confidence interval
HSR&D	Health Services Research and Development Service
OR	Odds ratio
P or p	Probability
VA	Veterans Affairs
VAMC	VA Medical Center
NSCLC	Non-small cell lung cancer
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ASCO	American Society of Clinical Oncology
TKI	Tyrosine Kinase Inhibitors